

**The Diagnosis of Osteoporosis Using Xtreme-CT Data:
The Development of a Protocol**

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Introduction

With the continual aging of populations in most industrialized countries reducing the morbidity and mortality of health issues affecting the elderly is becoming increasingly important. Osteoporosis is a disease leading to reduced bone mass and loss of trabecular structural integrity, increasing the risk of fracture. It is estimated that by 2025 total associated costs worldwide will reach \$ 45.6 billion [1]. Patients who suffer fractures, which are most common at the femoral neck and vertebrae, experience significant pain, loss of mobility and productivity, and reduction in life expectancy. A full 1 in 3 women, and 1 in 10 men, will experience some type of osteoporotic fracture in their lifetimes [2]. In fact, for a 50 year old postmenopausal white woman the lifetime chance of dying of complications of osteoporotic hip fracture are equal to the chances of dying from breast cancer [1].

Various pharmaceutical treatment options are available to those diagnosed with osteoporosis, as well as lifestyle and diet interventions. The effectiveness of these treatments is heavily dependent on early diagnosis of the disease though, as bone microstructural connectivity is irreplaceable and bone mass gains with treatment simply reinforce the remaining structures [3]. Unfortunately it is likely many patients will not be diagnosed sufficiently early since the disease is rarely symptomatic before significant bone loss has occurred. In fact, it is often not diagnosed until after the first fracture occurs [4]. Current techniques may not be offering the full range of data possible to effectively determine bone quality early in disease progression.

The recent introduction of High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT) scanners suitable for clinical use offer a new opportunity to improve the diagnostic process. Numerous studies have shown that the standard osteoporotic diagnosis measure, Bone Mineral Density (BMD), is insufficient to explain the entire range of trabecular bone strength and related fracture risk. It is necessary to broaden the scope of data considered in order to also include measures of microstructure, connectivity, and anisotropy [5, 6].

Background Information

In 1994 a World Health Organization study group proposed a diagnosis criteria that has become the standard clinical definition of osteoporosis. [7] The WHO guidelines compare measured bone mineral density (BMD) with average young healthy values, in terms of the number of standard deviations (SD) the patient's BMD is below the standard. Up to 1 SD below the healthy average is considered normal. Between 1 and 2.5 SD below is considered osteopenic (mild osteoporosis). 2.5 SD or lower is considered osteoporotic. A BMD more than 2.5 SD below the healthy average with detected fragility fracture(s) is labeled severe or 'established' osteoporosis [7]. It has been estimated that fracture risk at all sites increases at an approximately 1.7 ratio with SD decline of BMD [8]. For this standard scale BMD is measured with dual-energy X-ray absorptiometry (DXA). DXA uses two X-ray beams with specific distinct energy levels to enable soft tissue absorption to be subtracted out of the resulting images [7]. DXA is used to diagnose osteoporosis because it is the most widely used and studied, allowing patient scans to be compared to a extensive database of other scans.

The University of Calgary's Bone Imaging Laboratory owns one of the few Xtreme-CT [9] machines in North America. This medium sized Computed Tomography (CT) equipment allows more precise scanning at lower radiation levels than a standard, full-body, Computed Tomography (CT) machine, but can scan bones in vivo, unlike a micro-CT machine. This middle ground brings the accuracy and improved methods of laboratory machines typically used in cadaver or animal studies into the in vivo or clinical realm. CT machines work by taking many images from all direction around the subject, and reconstructing the results into a full model of the tissue. Rather than creating a simple 2-D X-Ray image like DXA, the Xtreme-CT builds a 3-D model of the scanned portion of bone.

The improved resolution of this new technology allows the accurate imaging of trabecular structure, as the voxel (3D pixel) size is now sufficiently small as compared to typical microstructures. Rather than having to indirectly derive most microstructural parameters, as has been necessary in past in vivo studies, measurements can be found directly using straight-forward image analysis. The standard parameters found directly from the scan include trabecular bone density, cortical bone density, average trabecular size, and average trabecular spacing. This expanded data set will hopefully make diagnosis of osteoporosis both more accurate and more meaningful.

Parameters provided by an XtremeCT exam:

Densities		Structure	
D100	Average Bone Density	BV/TV	Trabecular Bone Volume to Tissue Volume
Dtrab	Trabecular Bone Density	Tb.N	Number of Trabeculae
Dmeta	Meta Trabecular Bone Density	Tb.Th	Trabecular Thickness
Dinn	Inner Trabecular Bone Density	Tb.Sp	Trabecular Separation
Meta/Inn	Ratio Meta to Inner Density		
Dcort	Cortical Bone Density	C.Th	Cortical Thickness

Table 1: Brief Overview of Measured Parameters [9]

D100, Dtrab, Dmeta, Dinn, and Dcort measured in (mmHA/cm³), Meta/Inn and BV/TV are dimensionless (% in literature), Tb.N measured (/mm), Tb.Th, Tb.Sp, and C.Th measured in (mm).

A key difference between the BMD measured by DXA and the XtremeCT is the number of dimensions accounted for. The 2D image found with a DXA scan gives a mineral density per square area, whereas the 3D image found using the XtremeCT, or any other CT machine, give a mineral density per cubic volume. These two different measures are typically termed aBMD and vBMD [10]. The measurement of vBMD has both advantages and disadvantages to the measure of bone quality. One advantage is that it measures only a set depth of bone, which allows it to determine the density difference between cortical and trabecular bone. This in turn allows the quality and strength contribution of each different structural region to be analyzed separately, as well as avoiding the concealment of trabecular bone loss by the more dense cortical bone. On the other hand this measure ends up disregarding the overall macrostructure, or size, of the bone in its entirety, which is another important measure of bone strength.

The primary challenge presented in the attempt to use Xtreme-CT for osteoporosis diagnosis is the lack of a large set of normal or healthy scans to compare clinical scans to, and a lack of clearly defined diagnostic protocols. As mentioned before, the standard diagnostic practices rely on comparison to 'normal' or healthy young averages to gauge relative bone health. This relative technique is currently not possible with CT. While the machine shows very clearly the current status of the bone, there is no measure that determines what the status should be. Even if it is clear that there is a disease progression, such as in the case where fragility fractures are observed, there is no way to quantify its progress. The accurate data provided by the CT scan allows a close monitoring of changes in bone volume and structure over time with use of data registration and computer analysis, but offers few conclusions about the bone health at the starting point.

Another key challenge is the fact that the Xtreme-CT machine can only scan the body's extremities, namely the two arms and legs. The WHO organization criteria, and most osteoporosis knowledge, is based on BMD measurements in the Posterior-Anterior (PA) lumbar spine, and proximal femur. The challenge is therefore to correlate the peripheral data collected with core bone degeneration. Weight supporting bone tends to renew itself at a much faster rate than peripheral bone, and is typically more seriously affected by disease progression. Using standard imaging techniques, studies have shown a bone density loss of as little as 0.74 SD below the healthy average correlates to a PA lumbar spine and proximal femur density loss of more than 2.5 SD. This reduced sensitivity may make diagnosis less definite, but there is still a reasonably significant correlation between peripheral and core sites [7].

While the sensitivity of peripheral sites has been seen to be lower, and the correlations to core sites is not particularly strong, it has been determined that there is a significant relationship. Microstructural parameters measured at peripheral sites are particularly weak predictors of core bone microstructural parameters because different sites have very different structures. For example the pelvic girdle and vertebrae typically exhibit a primarily rod-like structure while the femoral neck and calcaneus typically show a primarily plate-like structure. Density related parameters such as BV/TV are much more strongly correlated. For BV/TV the correlation between the radius and lumbar spine has an r-value of 0.39 and the radius and femoral neck has a r-value of 0.25. This demonstrates a correlation strong enough to draw conclusions about key fracture risk sites based on analysis of peripheral scans [11].

The pharmaceutical options available to patients diagnosed with osteoporosis include drugs such as bisphosphonates (alendronate, ibandronate, risedronate), calcitonin, raloxifene, strontium ranelate, teriparatide and tibolone. These drugs work through various mechanisms to combat osteoporosis, bisphosphonates acting as reabsorption blockers to help reduce the volume of bone tissue removed as part of the body's continual bone remodeling. Raloxifene on the other hand acts as a selective estrogen receptor modulator, offsetting the hormonal causes of the disease [12]. Clinical studies have shown that

these pharmaceutical treatments are effective in increasing bone mass and strength [5, 13].

An interesting point that has come up in the course of the clinical assessment of various osteoporosis medications is the possible independence of bone strength and BMD. This was seen in the comparison of raloxifene and alendronate, both treatments which have shown to cause a reduction in fracture risk, the increase in BMD is much less with raloxifene (+3%) than with alendronate (+8%). Similar fracture reduction results were found with very different effects on BMD. Fluoride treatment on the other hand caused a major increase in BMD (+10%) but was not shown to reduce fracture risk [5, 13].

Further to this discussion of the value of BMD increase in predicting fracture risk, it would be worthwhile examining the effect changing bone mass has on various microstructural parameters. Trabecular bone is much more susceptible to bone loss than cortical bone due to its greater surface area. Bone reabsorption is carried out by the bone cells known as osteoclasts, which bore holes through mature bone. This bone destruction is part of normal bone regeneration and is usually balanced when the cavities are eventually refilled with new bone by another bone cell known as osteoblasts. This constant process of reabsorption and rebuilding allows bone structure and mass to adapt to changing environmental conditions. In the diseased state reabsorption out-paces rebuilding, and reduces bone mass, destroying structure. Since trabecular bone has a greater surface area it is more accessible to osteoclasts, and is the first to experience weakening as the disease progresses. More specifically, the typical form of bone loss through bone remodeling is the removal of horizontal struts in the trabecular bone. This will actually increase bone strength to weight ratios for loading in the longitudinal direction, but fracture risk due to buckling and small transverse loads increases dramatically [2]. Because of this arrangement it is difficult to relate changes in trabecular structure to simple measures of longitudinal elastic stiffnesses of bone [14]. It can then be seen that reductions in BMD first affect the degree of anisotropy (DA) and connective density (ConnD) of bone, and that these parameters are poor predictors of stiffness or ultimate stress. While these should theoretically be good indicators of disease progression, they cannot readily be relied on as significant weakening can occur without completely removing the structure. Since a measure like connective density responds to number of connections rather than quality of connections it will not show fracture risk well. A better measure of this removal of cross struts is trabecular number (Tb.N) ($r^2 = 0.42$ with σ_u). Conversely, when in response to drug therapy strength and BMD increase, the most affected parameters are those focusing on individual trabeculae, such as trabecular thickness (Tb.Th) ($r^2 = 0.59$ with BV/TV) and spacing (Tb.Sp) ($r^2 = 0.62$ with BV/TV). This is shown in Table 2, [4] where elastic modulus, yield stress, and ultimate stress are related to various microstructural parameters.

Table 2
 r^2 values between all mechanical and microstructural indices studied

	SI E	AP E	ML E	Bulk E	SI YS	SI US	BV/TV	ConnD	SMI	TbN	TbTh	TbSp	DA	
SI E	1.00	0.64	0.58	0.85	0.58	0.61	0.40	0.03	0.36	0.14	0.19	0.25	0.15	SI E
<i>p</i>								0.2012		0.0051	0.0008		0.0042	<i>p</i>
AP E		1.00	0.71	0.87	0.61	0.64	0.49	0.06	0.46	0.12	0.25	0.27	0.06	AP E
<i>p</i>								0.0741		0.0081			0.0796	<i>p</i>
ML E			1.00	0.86	0.64	0.67	0.58	0.02	0.05	0.30	0.26	0.46	0.04	ML E
<i>p</i>								0.3492					0.1206	<i>p</i>
Bulk E				1.00	0.69	0.74	0.54	0.03	0.49	0.23	0.26	0.37	0.10	Bulk E
<i>p</i>								0.2302		0.0003			0.0157	<i>p</i>
SI YS					1.00	0.98	0.79	0.14	0.85	0.40	0.19	0.66	0.27	SI YS
<i>p</i>								0.0204			0.0062			<i>p</i>
SI US						1.00	0.81	0.12	0.87	0.42	0.20	0.69	0.25	SI US
<i>p</i>								0.0319			0.0053			<i>p</i>
BV/TV							1.00	0.16	0.94	0.35	0.59	0.62	0.14	BV/TV
<i>p</i>								0.0024					0.0037	<i>p</i>
ConnD								1.00	0.20	0.14	0.26	0.01	0.23	ConnD
<i>p</i>									0.0005	0.0048		0.3609	0.0002	<i>p</i>
SMI									1.00	0.31	0.46	0.55	0.16	SMI
<i>p</i>													0.0026	<i>p</i>
TbN										1.00	0.02	0.88	0.04	TbN
<i>p</i>											0.3168		0.1252	<i>p</i>
TbTh											1.00	0.14	0.03	TbTh
<i>p</i>												0.0057	0.1997	<i>p</i>
TbSp												1.00	0.08	TbSp
<i>p</i>													0.0325	<i>p</i>
DA													1.00	DA
<i>p</i>														<i>p</i>

Note: r^2 values without associated p -values indicate $p < 0.0001$. Values in italics indicate $p > 0.05$.

Table 2 – Correlations Between Mechanical and Microstructural Parameters [4]

When evaluating bone quality is important to bear in mind certain key threshold values that affect the measurement of bone quality. It has been shown that trabecular thickness and separation have a non-linear relationship with bone volume ratios. At low bone volume it has been seen that trabecular thickness decreases and trabecular separation increases at a much greater relative rate than observed at high bone volume. This suggests that there exists a critical bone volume value below which structural integrity deteriorates rapidly leading to greater risk of fracture [15]. Also of note is the changing fracture mechanisms with variance in bone volume. It has been suggested that below 20% Bone Volume to Total Volume ratio (BV/TV) large-deformation failure mechanisms become very significant, accounting for up to 80% of strength reduction. When examining the onset of large-deformation failure mechanisms BV/TV is the strongest predictor, but other measures such as Structural Model Index (SMI) and Trabecular Thickness (Tb.Th) are also quick significant [16].

An important consideration in bone strength is the presence of resorption cavities in the trabeculae. As mentioned before osteoclasts bore holes or cavities through bone. It has been suggested that these cavities constitute a significant determining factor for bone strength [17, 18]. Their contribution to fracture risk is through increased stress concentrations in trabeculae, which fail much more readily than suggested by BMD measurement. The reduction in BMD by resorption cavities is very small compared to the amount of BMD loss by thinning that would give the same reduction in bone strength. It has been suggested that a 20% reduction in bone mass by thinning causes an approximately 30% reduction in bone strength, while the same bone mass loss by resorption cavities causes up to a 50% reduction [6].

It has also been suggested that it is necessary to consider bone mineral distribution in trabecular structure. The mineral content of bone is the component primarily responsible for its strength and stiffness in compression, making its distribution a relevant factor. Since new bone typically has less

mineral content and smaller mineral crystals, surface bone in trabeculae are generally less stiff than center bone, which is more mature. This is because bone growth happens relatively rapidly, while subsequent mineralization is fairly slow. This uneven mineral distribution gives a lower overall strength than a comparable structure with an even mineral distribution. Based on simple mechanical simulation this is clearly a much more significant factor in bending, than in axial compression. The structure of trabecular bone is sufficiently complex though, that compression of a region or sample of bone produces both compression and bending in different trabeculae. This effect is unclear, as it depends on how stiffness is assumed to be affected by mineralization, and even if some weakening is considered, the more ductile surface layer helps stop micro-cracking, negating some of the effect [19].

Proposed Approach

The proposed approach is a combination of contributions from various measurements taken from Xtreme-CT scans. The interactions between the considered parameters are complex, and dependent on which are being varied and in what direction. Since the purpose of this study was to determine bone quality from a single scan, the interactions measured between microstructural parameters and tissue properties will be focused on. Interactions in between the various parameters as disease or treatment progresses will be considered secondary. It has been shown that bone quality is dependent on a large number of different factors, so nearly any proposed measure will have to settle for an approximation based on the most important ones.

The first set of parameters considered will be those related to tissue density. This builds upon the past standard measurement of BMD. It follows fairly logically that since the mineral content of bone is the primary contributor to compressive strength at the micro-scale it will also be an important determinant of overall structural strength. The most obvious density related parameter measured by the Xtreme-CT system is D100 (mgHA/cm^3). This is a simple 3D extension of the concept of BMD. While it is the simplest measure available it forfeits much of the advantage afforded by high-resolution 3D scans, and as such will not be stressed. In its place we will consider the separate parameters of trabecular and cortical density. Another obvious choice for this category is the bone volume fraction BV/TV. A simple measure of how much of the trabecular bone region is actual bone tissue, it is probably the best researched parameter in the large emerging body of work looking at structural determinants of bone strength. As discussed before trabecular thickness is significantly affected by BMD increases, so it can for our purposes be considered a density related parameter. Based on its close correlation to ultimate stress, yield stress, and elastic modulus, and its well researched nature we can pick BV/TV as the best way to describe the density of the studied bone tissue.

The next set of parameters to consider are those reflecting the connectivity of the bone. This set largely consists of non-metric parameters not included in the standard Xtreme-CT output such as connective density. In addition to these we can consider trabecular spacing to also be a measure of connectivity, and microstructural quality. Osteoporosis affects the cross-struts in the trabecular architecture that lie perpendicular to the primary loading direction first. This progression can be clearly seen in the increasing space between stronger and thicker individual trabeculae in the loading direction. Drug therapy that helps restore bone mass typically leads to bone being added to existing structures rather than being formed into new trabeculae. Following this reasoning, we can also include trabecular number as a connectivity measure, as it is a related parameter that will be affected by loss of connecting members. It will reflect the true structural integrity of the bone better than either thickness or spacing. Based on the correlations seen above trabecular spacing will be the best choice to describe the connectivity in the sample bone tissue.

As a simple first approximation of bone quality, we can establish the contributions of each set of parameters based on the degree of variability left unexplained. It has been found that density leaves about 30% of variability in strength unexplained [4]. It can therefore be set to a weighting of 0.70 with the remainder attributed to connectivity, with a weighting of 0.30. Typical BV/TV in postmenopausal women not considered osteoporotic vary in literature from 13% to about 46% [11, 20, 21]. Typical trabecular number values again vary from 1/mm to 2.64/mm [11, 22]. Past research based on comparing fracture cases to control indicate an increased fracture risk at a ratio of 4.2 with a reduction of one SD in bone density, which in our case is represented by BV/TV. In the case of trabecular number the risk ratio with 1 SD drop is 2.3. [23]

A new baseline of microstructural parameters needs to be established using the new HR-pQCT machine, as literature values do not seem to agree on their typical values. This process is already underway at the University of Calgary, with a random sample of individuals being continually scanned. Even a fairly small sample size numbering anywhere over a couple hundred should give a preliminary estimate of these values, and begin to suggest how great their distribution is. As an initial step a simple linear relationship between fracture risk and standard deviations from the average could be used to determine bone quality. The diagnostic thresholds of the resultant scores can then be determined in comparison to the gold standard, DXA measured BMD.

$$4.2 * \frac{(BV / TV - BV / TV_o)}{SD_{BV / TV}} + 2.3 \frac{(Tb.N - Tb.N_o)}{SD_{Tb.N}} < Threshold$$

For this relationship the 0.7/0.3 weighting split discussed earlier is left out, since the fracture risk contributions enforce a similar relationship. Using these number the weighting is closer to 0.65/0.35. To refine the equation, cadaveric bone samples could be impact tested to simulate a fall from shoulder height. It could then be used on test subjects in comparison to DXA for validation.

Conclusion

Based on the previously discussed bone strength dynamics, any complete measure of bone quality will be fairly complicated. The proposed solution is a simplified approach that looks at only two parameters. This is the best approach suggested by literature, as these have been repeatedly highlighted as the most significant parameters. The amount of bone supporting a normal or impact load is the primary factor in fracture risk, and an additional structure factor helps improve the prediction. The inclusion of a greater number of standard Xtreme-CT determined parameters would add little to the estimate.

Based on the results of research it may be necessary to expand the range of variables considered in our quantification of bone quality beyond the straight-forward range provided. The effect of bone remodeling in particular has been seen as a key strength determining factor. The mass changes due to resorption cavities are very small, and difficult to account for in measures of density or mass, but can have significant structural effects. This also may have a significant effect on strength through mineral distributions. In order to account for these variables the possibility of including a urine or blood test should be considered, in order to be able to examine growth factors and hormones as part of the quality measure.

As is often the case in the examination of bone microstructure, it is difficult to determine the scale at which analysis is most effectively performed at. While macrostructural measures that treat bone as a continuum with averaged properties fail to account for many subtleties in bone quality, they do provide a fairly good estimate. As the level of detail is improved, new features can be examined and accounted for, there still remain key details that cannot be measured. Resorption cavities and micro-cracks are not included in current analysis. In the future when these can be accounted for, we will struggle to accurately measure other factors such as collagen and mineral crystal alignment. A more promising approach may be to approach the problem from the opposite direction, studying the mechanisms that give rise to the structures we have been examining, and include those factors as base causes in our quality measures.

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